II. The Claims Are Not Obvi us Under 35 U.S.C. § 103

Greenberger in vi w f *Crapo* and Applicants' Disclosure

The Office has rejected claims 47, 61-65, 67, 69-75, 78-79, and 81 under 35 USC § 103(a) as being obvious over *Greenberger* (U.S. Patent No. 5,599,712) ("*Greenberger*") in view of *Crapo et al.* (U.S. Patent No. 5,994,339) ("*Crapo*"), and Applicants' disclosure. (Office Action, pages 2-6.) Applicants respectfully traverse the rejection.

To establish a *prima facie* case of obviousness, there must be some reason, suggestion, or motivation in the prior art to lead one of ordinary skill in the art to modify or combine the teachings of the references in the manner proposed by the Office. *See Pro-Mold and Tool Co. v. Great Lakes Plastics, Inc.*, 75 F.3d 1568, 1573 (Fed. Cir. 1996); M.P.E.P. § 2143. The combination of references must also provide a reasonable expectation of success. *See In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). The suggestion or motivation must be found in the prior art, not in Applicant's disclosure. *See id.* And the suggestion to combine or modify the prior art teachings must be clear and particular. *See In re Dembiczak,* 175 F.3d 994, 999 (Fed. Cir. 1999). Thus, while a person of ordinary skill in the art may possess the requisite knowledge and ability to modify the prior art, that modification is not obvious unless the prior art suggested the desirability of such a modification. *See In re Gordon*, 733 F.2d 900, 902 (Fed. Cir. 1984).

Applicants contend that the Office has failed to establish a *prima facie* case of obviousness. There simply is no clear and particular suggestion in the prior art to combine *Greenberger's* teachings of protecting cells from the damaging effects of anti-cancer drugs and ionizing radiation using adenoviral vectors encoding an SOD

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gene with the disease states described in the secondary references, as proposed by the Office.

Greenberger is directed to "protecting an individual's tissues and cells against the damaging effects of an agent that elicits the production of a free radical, superoxide anion, or heavy metal cation when that individual is exposed to an agent." (Col. 1, lines 7-11.) Specifically, *Greenberger* concerns protecting a cancer patient's tissues and cells from the damaging effects of anti-cancer drugs and ionizing radiation. (Title, Abstract, and Col. 1, line 1, to Col. 3, line 15.) The Office alleges that *Greenberger* "teaches that it is a object of the invention to '...provide a safe and efficient method of transferring oxidation or cation-scavenging protein encoding genes directly into a patient's cells.'" (Office Action, page 3.) The Office admits that *Greenberger* "does not teach the use of the recited adenoviral vectors to treat the specific diseases recited by the applicants." (*Id.*, page 3.)

The Office alleges that the secondary references, *Crapo* and Applicants' specification, cure the deficiencies of *Greenberger* because they disclose that free radicals are recognized as being involved in certain diseases. (*Id.*) The Office concludes that it would have been obvious to combine *Greenberger*, *Crapo* and Applicants' disclosure

> because *Greenberger* et al. teaches that said vectors can be used to safely and efficiently deliver SOD genes to patients so as to scavenge excess free radicals which [*Crapo*] and applicants disclose are well known to be associated with diseases such as ALS, diabetes, etc.

(*Id.*, pages 4-5.)

Applicants, however, point out that the only "patients" that *Greenberger* teaches or suggests are cancer patients being treated with an agent that elicits the

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production of free radicals. *Greenberger* is specifically concerned with preventing the toxic effects of the exogenous agents (*i.e.,* chemotherapy and/or ionizing radiation) administered to the patients. As pointed out, the Office admits that *Greenberger* "does not teach the use of the recited adenoviral vectors to treat the specific diseases recited by the applicants." (*Id.*, page 3.) Moreover, Applicants submit that nothing in *Greenberger* teaches or suggests using *Greenberger*'s adenoviral vector for treating or preventing any disease. *Greenberger* merely discloses methods for preventing the toxic side-effects of exogenous anti-cancer therapies.

The Office alleges that *Crapo* "recites the use of sequences encoding SODs (EC-SODs and Cu/Zn SOD) and SOD mimetics to treat individuals suffering from diseases associated with excess free radicals (*e.g.* Parkinson's Disease, arteriosclerosis, Alzheimer's Disease, ALS, *etc.*) ... and that sequences encoding SOD molecules can be delivered to patients via viral vectors." *Id.* *Crapo* discloses three main families of known mammalian SODs: CuZn-SOD found in cytosol, Mn-SOD found in mitochondria, and EC-SOD found extracellularly. Col. 1, lines 37-44. Similarly, Applicants disclose these three families as SOD-1, SOD-2, and SOD-3, respectively. Page 7, lines 1-2. *Crapo*, however, is primarily concerned with the use of extracellular-SOD (EC-SOD) (SOD-3) and mimetics of EC-SOD. For example, *Crapo* suggests that the "relative deficiency of extracellular-SOD may result in greater susceptibility to extracellular oxidant stresses." Col. 1, lines 52-58. *Crapo* states that "[s]urprisingly, it has been found that EC-SOD increases, rather than decreases, central nervous system O_2 toxicity and that this effect of EC-SOD occurs through modulation of NO.." Col. 2, lines 30-34. In summarizing their invention, *Crapo* also states that "[t]he invention thus relates to methods of manipulating nitric

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oxide function that involve the use of extracellular antioxidants." Col. 2, lines 35-37. Accordingly, *Crapo*'s methods teach and suggest the use of EC-SOD and EC-SOD mimetics to modulate extracelular NO. and thereby treat various disorders.

The Office alleges that *Crapo* discloses use of Cu/Zn SOD to treat individuals suffering from diseases associated with excess free radicals. Office Action, page 3. Applicants disagree, and point out that *Crapo* discloses the use of a modified Cu/Zn SOD (SOD-1) sequence wherein "[f]urther proteinaceous agents suitable for use in the present method include chimeric proteins with targeted binding SOD activity, for example, Cu/Zn SOD linked to an EC-SOD binding sequence...." Col. 17, lines 51-55. It appears that *Crapo*'s EC-SOD binding sequence is intended to allow the chimeric protein to bind to the extracellular matrix and thereby impart EC-SOD mimetic extracellular activity. Applicants point out that the instant claims recite "an intracellular CuZn superoxide dismutase-1(SOD-1)." Accordingly, *Crapo* does not teach or suggest use of an intracellular CuZn superoxide dismutase-1 (SOD-1) of the instant claims.

Further, the evidence indicates that *Crapo*'s methods are specifically designed to target the bioavailability of NO. and extracellular levels of NO.. For example, *Crapo* states that

> NO. is an intercellular signal and, as such, NO. must traverse the extracellular matrix to exert its effects. No., however, is highly sensitive to inactivation mediated by O2- present in the extracellular spaces. EC-SOD is thus an enzyme ideally suited to increase the bioavailability of NO. by preventing its degradation by O2-.
>
> One embodiment of the present invention relates to a method of regulating extracellular NO. levels using polypeptides having EC-SOD activity. As indicated above, the invention also relates to mimetics of EC-SOD that can be targeted to strategic locations and to the use of such mimetics in manipulating extracellular levels of NO.."

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Col. 16, lines 14-26. Hence, *Crapo*'s methods rely upon the use of EC-SOD, EC-SOD mimetics, or polypeptides having EC-SOD activity to treat the disclosed diseases. Accordingly, Applicants submit that there is no motivation to combine *Greenberger*'s adenoviral vectors and intracellular SOD-1 with *Crapo*'s extracellular SOD or EC-SOD mimetic to treat diseases such as atherosclerosis, cardiovascular disease, diabetes, retinopathy, cataract formation, Parkinson's disease, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, 21 trisomy, and hypertension. Moreover, Applicants point out that there is no evidence of record that Applicants' claimed intracellular SOD-1 is a mimetic of EC-SOD or has EC-SOD activity.

Accordingly, the evidence does not suggest that one of ordinary skill reading the cited references would be motivated combine the cited references to use the adenoviral vectors and SOD-1 of *Greenberger* to treat the diseases disclosed in *Crapo* or Applicants' specification.

Furthermore, the Office points to Applicants disclosure at page 2 that it is "nowadays recognized that these free radicals are involved in [certain disorders or diseases]" as evidence of motivation to combine the cited references to devise the claimed invention. Applicants' disclosure at page 2, lines 8-17, however, merely recognizes that free radicals are involved in these disorders or diseases. Applicants submit that one of ordinary skill in the art would also know that that other mechanisms and pathways not directly related to free radicals are also important for the course and pathology of these disorders and diseases. Accordingly, Applicants' disclosure at page 2, lines 8-17, does not provide the Office with clear and particular

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evidence that one of ordinary skill reading the cited references would be motivated to combine the cited references to use the adenoviral vectors and SOD-1 of *Greenberger* to treat the diseases disclosed in *Crapo* or Applicants' specification.

In view of the above, Applicants contend that the Office has merely identified a combination that might be feasible, but has not proffered clear and particular evidence concerning the desirability of making the combination. Although *Greenberger*'s adenoviral vector may be useful for preventing the toxic effects of exogenous agents that generate free radicals, there is no clear and particular evidence that *Greenberger*'s vector would be similarly useful for treating *Crapo*'s diseases where excess free radicals or extracellular NO. may be involved in the disease mechanisms. Moreover, "a general incentive does not make obvious a particular result, nor does the existence of techniques by which those efforts can be carried out." *In re Deuel*, 51 F.3d 1552, 1559 (Fed. Cir. 1995). At best, it may have been obvious to try such a combination. However, obvious to try is not the standard. *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988); M.P.E.P. § 2145(X)(B).

Consequently, Applicants respectfully request reconsideration and withdrawal of the rejection because the claims are not *prima facie* obvious over the combined teachings of these references.

Greenberger in view of _Crapo_, Applicants' Disclosure, and _Gregory_

The Office has rejected claims 66, 82, and 83 under 35 USC § 103(a) as being obvious over *Greenberger* in view of *Crapo*, Applicants' disclosure, and *Gregory et al.* (U.S. Patent No. 5,882,877) ("*Gregory*"). (Office Action, pages 5-6.) Applicants respectfully traverse the rejection.

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Applicants' above remarks regarding the lack of motivation to combine *Greenberger, Crapo*, and Applicants' specification apply to the present rejection.

Applicants submit that the additional combination with *Gregory* does not cure the deficiencies of the combination of *Greenberger, Crapo*, and Applicants' specification. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

Greenberger* in view of *Crapo*, Applicants' Disclosure, *Le Gal La Salle*, and *Nabel

The Office has rejected claims 68 under 35 USC § 103(a) as being obvious over *Greenberger* in view of *Crapo*, Applicants' disclosure, *Le Gal La Salle et al., Science* 259:988-990 (1993) ("*Le Gal La Salle*"), and *Nabel et al.* (U.S. Patent No. 5,650,306) ("*Nabel*"). (Office Action, pages 6-7.) Applicants respectfully traverse the rejection.

Applicants' above remarks regarding the lack of motivation to combine *Greenberger, Crapo*, and Applicants' specification apply to the present rejection.

Applicants submit that *Le Gal La Salle* and *Nabel*, either together or separately, do not cure the deficiencies of the combination of *Greenberger, Crapo*, and Applicants' specification. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

III. CONCLUSION

In view of the foregoing, Applicants respectfully request that the Office reconsider and withdraw the rejections of pending claims 47, 61-75, 78-79, and 81-83 as obvious over the cited art, and allow all pending claims.

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Please grant any extensions of time required to enter this amendment and response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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